

**REMARKS**

This paper is responsive to the Non-Final Rejection dated October 02, 2007. Claims 1-16 were pending in the present application. With this amendment, previously pending claims 1-57 have been canceled, and new claims 58-83 have been added. Applicants expressly reserve the right to pursue any canceled subject matter in one or more related, continuation, divisional or continuation-in-part application(s).

The Applicants invention is directed to optical labeling molecules with positive and negative charge moieties added to a neutral or a charged dye to obtain a net neutral charge on a zwitterionic dye moiety. The non-titratable zwitterionic dyes of the invention are useful as labeling molecules with increased detection sensitivity, increased solubility and recovery of intact proteins without perturbing the target proteins isoelectric point.

Support for the new claims can be found throughout the specification, including the claims of the application as originally filed. Support for new claim 58 can be found in the originally filed claim 1, and in the specification on page 5, lines 21-32; page 6, lines 13-15, and 26-28; page 8, lines 24-36; page 9, lines 4-15; page 12, lines 5-22, and page 14, lines 5-15, and 30-37.

Support for new claim 59 can be found in the specification on page 8, lines 17-18. Support for new claim 60 can be found in the specification on page 13, lines 9-12, and page 14, lines 4-8. Support for new claim 61 can be found in the specification on page 14, lines 18-29, and Figure 8A. Support for new claims 62-63 can be found in the specification on page 12, lines 18-22. Support for new claim 64 can be found in the specification on page 17, lines 22-34.

Support for new claim 65 can be found in the specification on page 17, lines 22-34. Support for new claim 66 can be found in the originally filed claims 3-5. Support for new claim 67 can be found in the originally filed claim 9. Support for new claim 68 can be found in the originally filed claim 8. Support for new claim 69 can be found in the originally filed claim 10, and in the specification on page 12, lines 18-26 and on page 14, lines 11-15. Support for new claims 70-75 can be found in the originally filed claims 11-15.

Support for the new claim 76 can be found in the originally filed claim 1, and in the specification on page 5, lines 21-26; page 6, lines 13-15, and 26-28; page 9, lines 4-15; page 12, lines 5-22, and page 14, lines 18-37 and Figure 8A. Support for new claim 77 can be

found in the specification as compound C in Figure 8A. Support for new claim 78 can be found in the specification in Figures 7A-10B. Support for new claim 79 can be found in the specification on page 15, lines 3-10, and page 16, lines 25-30. Support for new claim 80 can be found in the originally filed claim 16, and in the specification on page 16, lines 25-30. Support for new claim 81 can be found in the specification on page 16, lines 25-30. Support for new claims 82 and 83 can be found in the specification on pages 25-36, Examples 1-2.

Applicants assert that no new matter has been introduced by these amendments. Further, entry of the remarks and amendments submitted herein and reconsideration of the claimed subject matter is respectfully requested.

Applicants also request that the Examiner consider the **species of compound C of Figure 8A**, elected by Applicants in response to the Office's requirement for election of species now in claim 77, which was withdrawn by the Examiner in the Non-Final Rejection dated October 02, 2007. Since the Examiner examined the previously presented broad generic claim 1 (now claim 58), Applicants respectfully submit that the Examiner kindly examine the species included in the new claim 58 and presented herein since all species are encompassed by the new generic claim 58.

Claims 58-83 are currently pending in this application.

**Response to Rejections under 35 U.S.C. 112 (second paragraph)**

Claim 10 was rejected under 35 U.S.C. 112 (second paragraph) as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner alleges that the trademark "BODIPY" is not permitted in the claims.

In an effort to clearly claim Applicants invention, new claims 69 and 75 have been amended to recite the chemical name of "boron difluoride diaza-indacene-propionic acid preceding the trademark "BODIPY" in parenthesis.

**Response to Rejections under 35 U.S.C. 102**

**1. Benson *et al.* (US 6,051,719, “‘719”)**

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Benson *et al.* (US 6,051,719, “‘719”). Applicants respectfully submit that ‘719 does not support a *prima facie* case of anticipation for at least the following reasons:

‘719 does not teach each and every limitation set forth in claim 58, either expressly or inherently in its disclosure. Specifically, ‘719 does not teach a zwitterionic dye moiety further comprising at least one positive or at least one negative charge moiety wherein the said positive charge moiety is selected from a group consisting of a quarternary ammonium group, a guanidinium group and a positive charge group, and wherein said positively charge moiety is not titratable between the pH of 3-12, wherein the negative charge moiety is not titratable between the pH of 3-12 and is either a sulfonate group or a sulfate group; and wherein the positive and negative charge moieties are added (emphasis added) to finally obtain a net neutral optical labeling molecule.

While ‘719 teaches dibenzorhodamine-based dye compounds, it does not teach the further addition of at least one positive charge moiety or at least one negative charge moiety to the fluorescence dye (emphasis added), wherein such moieties can only be selected from the Markush group recited in claim 58.

Further, ‘719 also does not teach a titratable group moiety wherein the titratable group closely approximates the pK of the group removed from the analyte by reaction with the functional linker.

For all of these reasons, Applicants further submit that the new claims are not anticipated by the cited art and request that the rejection under 35 U.S.C. 102(b) be withdrawn.

**2. Haughland *et al.* (US 4,774,339, “‘339”)**

Claim 1 is also rejected under 35 U.S.C. 102(b) as being anticipated by Haughland *et al.* (US 4,774,339, “‘339”). Applicants respectfully submit that ‘339 does not support a *prima facie* case of anticipation for the reasons stated below.

While ‘339 discloses BODIPY-based dye compounds, it does not teach the further addition of positive charge moieties or negative charge moieties to the BODIPY, wherein such moieties can only be selected from the Markush group recited in claim 58 (emphasis

added). Further, there is no teaching of the structure or function of a titratable group which modifies the BODIPY dye so as to mimic the pK of the group removed from the target analyte by reaction with the functional linkers of the optical labeling molecule.

For all of these reasons, Applicants further submit that the new claims are not anticipated by the cited art and request that the rejection under 35 U.S.C. 102(b) be withdrawn.

Therefore, Applicants submit that neither '719 or '339 anticipate the structural characteristics of the claimed invention in the pending claims and respectfully request that these rejections should be withdrawn.

**Response to Rejection under 35 U.S.C. 102/103**

Claims 1-16 are rejected under 35 U.S.C. 102/103 as anticipated by or in the alternative obvious over Haughland *et al.* (US 6,972,326; "'326"). Applicants respectfully submit that this rejection is moot in light of the cancellation of claim 1 and the submission of the new set of pending claims.

Applicants respectfully submit that '326 does not teach each and every limitation set forth in claim 58, either expressly or inherently in its disclosure for all of the reasons set forth above under 35 U.S.C. 102. Thus, '326 does not expressly anticipate the structural characteristics of the claimed invention.

Further, Applicants submit that '326 does not alternatively, suggest, teach or make obvious the claimed invention. The claimed invention is drawn to a combination of a fluorescent dye modified by one or more positive or negative charge moieties, titratable group moiety, functional linker moiety, all working together to avoid perturbing the isoelectric point of the labeled protein in an effort to facilitate the isolation and characterization of labeled proteins.

The claimed molecules are optical labeling molecules that contain a zwitterionic dye moiety possessing additional positive or negative charge moieties which are added to a dye moiety to obtain a useful zwitterionic dye moiety with enhanced properties for increased aqueous solubility over a wide pH range and enhanced detection sensitivity (page 7, lines 35-37). Additionally, these molecules are prevented from entering biological membranes or hydrophobic spaces, thereby permitting such molecules to be used for labeling exposed proteins in solution (see specification, page 23, lines 13-16). The present invention provides

an improved optical labeling molecule that is not suggested by '326. The '326 patent does not suggest adding additional pairs of positive and negative charge moieties to BODIPY because there is no recognition in '326 that BODIPY's solubility or sensitivity needs to be improved. In fact, '326 teaches away from the claimed invention by using BODIPY dyes for a very different purpose (emphasis added), i.e., label poly(amino acids) immobilized on a solid support (column 4, lines 55-62).

For the reasons above, the disclosure of '326 and the claimed invention are so different, and there is no reasonable suggestion of motivation in '326 to render the optical molecules disclosed therein for the claimed purpose, without changing the respective principles of operation.

### **Conclusion**

For the reasons stated above, Applicant respectfully submits that the claims are now in condition for allowance, early notice of which would be appreciated. Should the Examiner disagree, Applicant respectfully requests a telephonic or in-person interview with the undersigned attorney to discuss any remaining issues and to expedite the eventual allowance of the claims.


Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-1283. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. 1.136(a)(3).

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